Primary safety endpoint - Survival

Survival was monitored for all randomized patients as a safety variable to determine if the survival estimates for Aredia patients were at least as good as those for placebo patients. The sponsor stated that no significant difference was found in the survival rates between the Aredia and the placebo treatment groups for all randomized patients. The median survival were 23.5 months (95%CI: 18.7 - 27.4 months) in placebo and 23.2 months (95%CI: 19.3 - 25.8 months) in Aredia. The sponsor stated that none of the deaths were considered to be trial-drug-related (11% in placebo and 19% in Aredia).

Efficacy related endpoints used at the end of the core phase

Skeletal morbidity rate (SMR=#SRE/year)

The raw and modified skeletal morbidity rates (-HCM) by 12 months were nearly statistically significantly (p=.051 and p=.056, Wilcoxon rank sum test, see Table 4S) lower in Aredia than in placebo. This is the protocol defined primary efficacy endpoint analysis. For the calculation of the SMR, events occurring at visits 3-15 for Core phase or visits 3-27 for Core+Extension phase were counted and normalized to 28 days then multiplied by 12 to show the event rate per year. There were a total of 467 SRE(-HCM) in Aredia and 627 in placebo at the end of the extension phase. When these episodes were analyzed by specific types, except for

Table 4S. Summary of SMR(+/-HCM) and individual type of SMR(Trial 18)

Ared. Plac. n=182 n=189	3-mon Are Pbo	6-mon Are Pbo	9-mon Are Pbo	12-mon Are Pbo	15-mon Are Pbo	18-mon Are Pbo	21-mon Are Pbo	24-mon Are Pbo
SMR-HCM(/yr)								
Median	0 0	0 0	0 1	**0 1**	0.7 0.9	0.6 1.2	0.5 1.1	0.5 1.4
Mean	2.7 2.9	2.6 3.1	2.3 3.2	**2.4 3.5**	2.4 3.6	2.4 3.6	2.4 3.6	2.4 3.6
p-value*	p=.856	p=.403	p=.160	**p=.051#**	p=.047	p=.043	p=.035	p=.021
p-value**	p=.959	p=.443	p=.171	p=.056	p=.041	p=.039	p=.026	p=.016
SMR+HCM(/yr)								
Median	0 0	0 0	0 1.1	0 0	0.7 1.5	0.6 1.2	0.5 1.3	0.6 1.5
Mean	2.7 3.0	2.6 3.2	2.3 3.3	2.4 3.6	2.5 3.7	2.4 3.7	2.4 3.8	2.4 3.8
p-value*	p=.783	p=.356	p=.117	p=.028	p=.027	p=.023	p=.020	p=.008
Path.Frac.(/yr)								
Median	na	na	na	na	0.0 0.7	0.0 0.6	0.0 0.5	0.0 0.5
Mean					1.7 2.2	1.6 2.2	1.6 2.2	1.6 2.2
p-value*					p=.043	p=.044	p=.056	p=.040
Radi.t.bone(/yr)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.50 1.1	0.6 1.0	0.6 1.1	0.6 1.1	0.6 1.1	0.6 1.1	0.6 1.2	0.6 1.2
p-value*	p=.017	p=.015	p=.005	p=.005	p=.018	p=.024	p=.017	p=.013
Radi.t.bone(/yr) (pain reli.)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.4 0.9	0.4 0.8	0.4 0.9	0.4 0.9	0.4 0.9	0.5 0.9	0.5 0.9	0.5 0.9
p-value*	p=.012	p=.012	p=.005	p=.006	p=.015	p=.025	p=.018	p=.011

the protocol defined primary efficacy analysis
na: not available
* Wilcoxon-rank-sum test (raw SMR)
** Wilcoxon-rank-sum test (modified SMR)

pathological fracture, the Aredia group had lower event rates with p-value <.05 by 24 months as well as by 12 months in radiation to bone and radiation to bone for pain relief.

Proportion of patients with at least one skeletal related event

Table 5S. Proportion of patients having any SRE(+/-HCM) (Trial 18)

Ared. Plac. n=182 n=189	3-mon Are Pbo	6-mon Are Pbo	9-mon Are Pbo	12-mon Are Pbo	15-mon Are Pbo	18-mon Are Pbo	21-mon Are Pbo	24-mon Are Pbo
Any SRE-HCM								
Proportion	32% 34%	42% 47%	45% 52%	47% 55%	51% 58%	52% 60%	53% 61%	55% 63%
95%CI for diff (Pbo-Are)	(-8%, 12%)	(-5%, 15%)	(-3%, 17%)	(-2%, 18%)	(-3%,18%)	(-2%,18%)	(-1%,19%)	(-1%,19%)
Chi-square test	p=.687	p=.302	p=.190	p=.109	p=.139	p=.115	p=.093	p=.094
Any SRE+HCM								
Proportion	32% 35%	42% 48%	46% 53%	47% 57%	52% 60%	53% 62%	54% 64%	56% 67%
95%CI for diff (Pbo-Are)	(-7%, 12%)	(-4%, 16%)	(-2%, 18%)	(-0%, 20%)	(-1%,19%)	(-0%,20%)	(0%,20%)	(1%,21%)
Chi-square test	p=.610	p=.259	p=.131	p=.057	p=.093	p=.059	p=.046	p=.027

The proportion of any SRE(-HCM) was not statistically significantly lower in Aredia (47%) than in placebo (55%) (p=.109, Chi-square test) by 12 months and by 24 months (63% in placebo and 55% in Aredia, p=.094). The sponsor performed stratified analyses and stated that "none of the Cochran-Mantel Haenszel tests for between-treatment differences in the proportions adjusting for a specific prognostic subgroup yielded a p-value ≤ 0.05." The sponsor also performed logistic regression models containing all the prognostic factors as main effects, none of the main effects were statistically significant. The results of these analyses were consistent with the unadjusted analysis, i.e., there is no statistically significant difference of the proportion of patients having an SRE between Aredia and placebo.

Time to first skeletal related event

Time to first SRE(-HCM) was not statistically significantly different between placebo and Aredia (7.4 months vs. 10.9 months; p=.118, log-rank test, see Table 6S) by 24 months. Time to first SRE(-HCM) was calculated as time from visit 2 (first drug administration date) to the

Table 6S. Time to first SRE analysis for Trial 18

Aredia (N=182) Placebo (N=189)	At the end of 12-months Aredia	Placebo	At the end of 24-months Aredia	Placebo
Time to first SRE(-HCM)(mon)				
Median	10.9	7.4	10.9	7.4
(95% CI)	(6.6, -)	(6.0, 11.5)	(6.4, 17.0)	(6.0, 11.5)
Censoring	57%	44%	45%	37%
log-rank test	P=.163		P=.118	

minimum of time to first fracture, time to first spinal cord compression/collapse, time to first radiation to bone, and time to first surgery to bone. The censoring rates were 37% in placebo vs.

45% in Aredia. Of those censored patients, 28% (placebo) vs 37% (Aredia) completed the core phase and the extension phase without an SRE.

3. REVIEWER'S EVALUATIONS AND COMMENTS

- Survival and time to discontinuation

The primary objective for the extension phase (the second 12 months) of these trials is the long-term survival and safety. Due to high dropout rates by the end of study periods, this reviewer performed the analyses of time to discontinuation, survival by 2-year and survival by study cut-off. The results are shown in Table 1R. For survival analysis, 2-year survival is defined as the time from first treatment administration to visit-27 (approximately 24 months) and study cut-off survival is defined as the time from first treatment administration to the study cut-off date. In the chemotherapy study (Trial 19) and the hormonal therapy study (Trial 18), it appeared that there is no statistically significant difference in survival either by 2-year or by study cut-off. The censoring rates are similar in both analyses. This reviewer confirmed the sponsor's survival results for Trial 18 and with a minor difference for Trial 19.

Table 1R. Survival and Time to discontinuation based on 2-year study vs. study cut-off

	Trial 19@			Trial 18^		
TRT n	Are 185	Pbo 195	p-value	Are 182	Pbo 189	p-value
Time to discontinuation* Median (months) 95%CI Censor	12.2 (10.3, 14.1) 25%	9.5 (7.7, 11.0) 18%	.035	16.3 (14.0, 19.9) 37%	13.6 (11.2, 17.3) 34%	.253
Survival by extension phase** 25th percentile (months) 95%CI Censor	19.9 (12.8, NR) 82%	NR (13.4, NR) 86%	.741	20.0 (15.5, NR) 80%	NR (24.8, NR) 89%	.073
Survival *** Median (months) 95%CI Censor	14.8 (12.6, 19.9) 14%	13.9 (11.7, 16.8) 14%	.653	23.2 (19.3, 25.8) 29%	23.5 (18.7, 27.4) 32%	.685

* time to discontinuation by the end of the extension phase (24 months)
** survival up to the end of the extension phase (24 months)
*** survival up to the end of the study cut-off
@Trial 19: study cut-off (03/21/96); Trial accrual periods (1/3/91-3/1/94)
^ Trial 18: study cut-off (07/01/96); Trial accrual periods (12/21/90-3/94)
NR: estimates not reached yet

For time to discontinuation, a patient is defined as censored if the final visit is 27 (approximately 24-month) or greater, and time to discontinuation is the time from the second visit date (first treatment administration) to last visit date. Both the chemotherapy trial and the hormonal therapy trial showed that on average, Aredia treated patients had a numerically longer time to discontinuation than placebo treated patients.

- Efficacy related endpoints used at the end of 12-month (the core phase)

Table 2R summarizes the sponsor's results, confirmed by this reviewer, on SMR(-HCM) by the end of the core phase (the primary efficacy endpoint) and by the end of the extension phase for Trials 18 and 19 and the related endpoints of secondary interest, viz., the proportion of patients with at least one SRE(-HCM) and time to first SRE(-HCM).

The SMR(-HCM) by 12 months was shown statistically significantly lower in the Aredia group compared to the placebo group in chemotherapy trial with p=.004, Wilcoxon rank sum test. The results were consistent with the analyses of proportions (p=.008, Chi-square test) or time to first SRE(-HCM) (p=.005, log-rank test). For long-term evaluation, the results of efficacy found at the end of the core phase were consistent with the results based on both phases I and II in terms of statistical evidence. In the hormonal therapy trial, SMR(-HCM) by 12 months appeared to be marginally significant (p=.051, Wilcoxon rank sum test). Neither the proportion of patients with at least one SRE(-HCM) nor the time to first SRE(-HCM) reached statistical significance at the end of the core phase (proportion: p=.109, Chi-square test; TTSRE: p=.163, log-rank test) and at the end of the extension phase (proportion: p=.094, Chi-square test; TTSRE: p=.118, log-rank test). Although the results for SMR(-HCM) showed a statistically significantly lower rate for Aredia compared to placebo at the end of the extension phase, it was not the primary objective for the extension phase of the trials. These studies are designed to study the treatment efficacy at

Table 2R. Efficacy related endpoints comparison across both phases of the trials#

	Trial 19-1 core phase by 12 months		Trial 19-2 core+extension by 24 months		Trial 18 core phase by 12 months		Trial 18 core+extension by 24 months	
Efficacy Parameter	Are n=185	Pbo n=195	Are n=185	Pbo n=195	Are n=182	Pbo n=189	Are n=182	Pbo n=189
SMR(-HCM)*								
Median(/yr)	0.0	1.0	0.0	1.8	0.0	1.0	0.5	1.4
Mean(/yr)	2.5	3.3	2.5	3.7	2.4	3.5	2.4	3.6
WRS test	(p=.004)		(p<.001)		(p=.051)		(p=.021)	
P**	43%	56%	46%	65%	47%	55%	55%	63%
Chi-square test	(p=.008)		(p<.001)		(p=.109)		(p=.094)	
P***	72%	83%	73%	89%	71%	75%	75%	83%
Chi-square test	(p=.013)		(p=.001)		(p=.491)		(p=.086)	
TTSRE(mons)***	13.1	7.0	13.9	7.0	10.9	7.4	10.9	7.4
log-rank test	(p=.005)		(p<.001)		(p=.163)		(p=.118)	

\# Summary of sponsor's results.

* # of SRE excluding HCM by 12 months is the protocol defined primary endpoint.

** Proportion of patients with at least one SRE(-HCM).

*** Patients prematurely discontinued without an SRE were assigned an event failure regardless of their treatment assignments, i.e., assuming random discontinuation (this reviewer's analysis).

**** Time to first SRE(-HCM) in months.

the end of the core phase, not considering the core phase as an interim analysis and the extension phase as the final analysis.

- Robustness ITT analysis

After discussion with Dr. Gang Chen, Team Leader of Biometrics for Oncology, this reviewer performed a robustness analysis on the secondary endpoint of "the proportion of at least one SRE" by assigning those patients event failures if they were prematurely discontinued from the study without an SRE. The assignments, based on the assumption of random discontinuation supported by similar premature discontinuation rates between Aredia and placebo, were equally applied to both treatment arms. Results were shown in the fifth row of Table 2R. Since the %s of patients prematurely discontinued without an SRE were similar between Aredia and placebo either by the end of the core phase (Trial 19: 29% in Aredia and 26% in placebo; Trial 18: 25% in Aredia and 20% in placebo) or by the end of the extension phase (Trial 19: 26% in Aredia and 25% in placebo; Trial 18: 20% in Aredia and 19% in placebo), results obtained appeared to further support the primary efficacy findings seen by the end of the core phase. The proportions of at least one SRE in the robustness analysis became 72% in Aredia and 83% in placebo (p=.013) by the end of the core phase, 73% in Aredia and 89% in placebo (p=.001) by the end of the extension phase for Trial 19, and were 71% in Aredia and 75% in placebo (p=.491) by the end of the core phase, 75% in Aredia and 83% in placebo (p=.086) by the end of the extension phase for Trial 18. The statistical significance seen in the robustness analysis of proportion was consistent with the analysis of proportion.

- sponsor's proposal to

From this reviewer's evaluations summarized in Table 2R, it appeared that the estimated effect of Aredia (seen in numerical differences) by the end of the extension phase is different between the chemotherapy treated patients and the hormonally treated patients. The results of efficacy found at the end of the core phase were consistent with the results based on both phases I and II in terms of statistical evidence. This applies to both chemotherapy treated patients and the hormonally treated patients.

In the chemotherapy trial, the treatment estimates seen from the efficacy related endpoints was stable or numerically improved in Aredia but no change in time to event or progressed with more events in placebo. In addition, the estimated treatment difference (Aredia - placebo) in median SMR(-HCM) improved from -1.0/yr by the end of the core phase to -1.8/yr by the end of the extension phase. Similarly, the estimated treatment difference (Aredia - placebo) in proportion of patients with at least one SRE(-HCM) improved from -13% the end of the core phase to -19% by the end of the extension phase. The estimated treatment difference in median time to first SRE(-HCM) increased from 6.1 months to 6.9 months. The efficacy related results in terms of estimated treatment improvement seen by the end of the extension phase further supported the finding seen by the end of the core phase.

In the hormonal therapy trial, however, the treatment estimates seen from the efficacy related endpoints was no change in time to event or progressed with more events in both Aredia and placebo. In addition, the estimated treatment difference (Aredia - placebo) in median SMR(-HCM) was -1.0/yr by the end of the core phase and -0.9/yr by the end of the extension phase. Similarly, the estimated treatment difference in proportion of patients with at least one SRE(-HCM) was 8% by the end of the core phase and 8% by the end of the extension phase. The estimated treatment difference in median time to first SRE(-HCM) was no difference (3.5 months) by the end of the core phase and by the end of the extension phase. The efficacy related results in terms of estimated treatment difference seen by the end of the extension phase were essentially no different from those seen by the end of the core phase.

- **Completers vs. Incompleters**

To address the issues of "Is late benefit firmly established ?" raised by the medical reviewer, Dr. Grant Williams, and "In patients who completed the phase I of the trial, what is the treatment effect considering phase II as a new trial?" raised by the medical team leader, Dr. John Johnson, during the course of the original statistical review (7/12/96), this reviewer reported the results by subdividing the Completers vs. Incompleters in the same way as in the original statistical review.

The premature discontinuation rates were very high in both trials. The dropout rate was a little higher in the placebo group compared to the Aredia group. In the chemotherapy trial, the dropout rates were 60% (placebo) vs. 52% (Aredia) at the end of the core phase and 85% (placebo) vs. 76% (Aredia) at the end of the extension phase. In the hormonal therapy trial, these rates were 48% (placebo) vs. 38% (Aredia) at the end of the core phase and 67% (placebo) vs. 63% (Aredia) at the end of the extension phase. This reviewer performed the survival analysis and the efficacy analysis based on patients' discontinuation status by the end of the core phase and/or by the end of the extension phase. The results are summarized in Table 3R (Trial 19) and Table 4R (Trial 18). The p-values shown in Tables 3R and 4R are for information only.

Table 3R.Primary efficacy comparison (classified by patients' discontinuation status) - Trial-19

Trial 19	didn't complete core phase (12 months)			Completed core phase but didn't complete extension phase			didn't complete core phase or extension phase (Incompleters)			Completed extension phase 24mon (Completers)		
TRT n	Are 86	Pbo 113	p-val	Are 52	Pbo 47	p-val	Are 138	Pbo 160	p-val	Are 47	Pbo 35	p-val
p*	43%	58%	.043	48%	91%	.0001	45%	67.5%	.0001	51%	51%	.974
SMR-HCM** Median Mean	0/yr 1.5/yr	1/yr 2.3/yr	.041	0/yr 2.6/yr	1/yr 2.2/yr	.0001	0/yr 2/yr	2/yr 3.2/yr	.0001	1/yr 2.2/yr	1/yr 2.3/yr	.811

* Proportion of patients with at least one SRE excluding HCM, the sponsor used this parameter to estimate the sample size (Chi-square test)
** # of SRE excluding HCM/time on study (per year); the protocol defined primary endpoint (Wilcoxon rank sum test)

In the chemotherapy trial, the SMR(-HCM) rate was statistically significantly lower with Aredia (p=.004). Both Aredia and placebo showed a similar median SMR(-HCM) of one skeletal related

event per year and a similar proportion (51%) of at least one SRE(-HCM) in patients who completed the entire 2-year trial (see the fourth category of Table 3R). Aredia effect shown was primarily on those patients who didn't complete either the core phase and/or the extension phase. Of specific note, among those patients who completed the core phase but didn't complete the extension phase, 91% of the placebo treated patients vs. 48% of the Aredia treated patients developed at least one SRE(-HCM) event.

Table 4R.Primary efficacy comparison (classified by patients' discontinuation status) - Trial-18

Trial 18	didn't complete core phase (12 months)			Completed core phase but didn't complete extension phase			didn't complete core phase or extension phase (Incompleters)			Completed extension phase 24mon (Completers)		
TRT n	Are 58	Pbo 84	p-val	Are 56	Pbo 40	p-val	Are 114	Pbo 124	p-val	Are 68	Pbo 65	p-val
P*	40%	57%	.040	71%	67.5%	.679	55%	60%	.433	54%	69%	.079
SMR-HCM** Median Mean	0/yr 1.8/yr	1/yr 2.3/yr	.114	2.5/yr 3.8/yr	3/yr 4.5/yr	.777	1/yr 2.8/yr	1/yr 3/yr	.566	1/yr 2.2/yr	2/yr 3.8/yr	.045

* Proportion of patients with at least one SRE excluding HCM (Chi-square test)
(Parameter used to estimate the sample size)
** # of SRE excluding HCM/time on study (per year)
(protocol defined primary endpoint) (Wilcoxon rank sum test)

In the hormonal therapy trial, however, the SMR(-HCM) rate was marginally significantly lower (p=.051) with Aredia. Those patients who completed both the core phase and the extension phase of the trial appeared to show a numerically improved trend in favor of Aredia: median SMRs(-HCM) were 1/yr for Aredia and 2/yr for placebo; proportions of at least one SRE(-HCM) were 54% for Aredia and 69% for placebo, see the fourth category of Table 4R. In contrast, both Aredia and placebo showed a similar median SMR(-HCM) of one skeletal related event per year and a similar proportion (55% for Aredia and 60% for placebo) of at least one SRE(-HCM) in patients who did not complete the core phase and/or the extension phase of the trial (the third category of Table 4R).

OVERALL SUMMARY AND CONCLUSIONS

The two pivotal studies were designed to show a lower skeletal morbidity rate (SMR) in the Aredia group by the end of the core phase in chemotherapy treated patients (Trials 19) and hormonally treated patients (Trial 18). They are in support of an application for palliative treatment for osteolytic bone metastases when given in addition to antineoplastic therapy. The major objectives for the extension phase of the trials were the long-term survival and safety. This review focuses on the extension phase of the trial.

In both the chemotherapy trial and the hormonal therapy trial, demographic and important prognostic characteristics including quality of life at baseline appeared to be reasonably matched between the Aredia group and the placebo group. In the chemotherapy trial, the median age for Aredia treated patients were 7 years older than placebo treated patients in stratum 2 (worse

ECOG baseline values). Premature discontinuation rates were a little lower in Aredia than in placebo, 76% vs. 85% in the chemotherapy trial and 63% vs. 67% in the hormonal therapy trial. Reasons for discontinuation were similar with the exception of a numerically higher rate of unsatisfactory therapeutic response with placebo (19%) than with Aredia (10%) in Protocol 19 and a numerically higher death rate with Aredia (19%) than with placebo (11%) in Protocol 18. The sponsor stated that the deaths were not treatment related.

A statistically significantly lower SMR(-HCM) rate, a smaller proportion, and a longer time to first skeletal related event (TTSRE) were demonstrated in Aredia treated patients in Trial 19. In the hormonal therapy trial, the Aredia group appeared to have a marginally significantly lower SMR(-HCM) rate by 12 months (p=.051) but there was no significant difference in proportion or in TTSRE by 12 months. Long-term survival and censoring rates were similar between Aredia and placebo. The median survival was 14.8 months for Aredia and 13.9 months for placebo in the chemotherapy trial and 23.2 months for Aredia and 23.5 months for placebo in the hormonal therapy trial.

In the chemotherapy trial, the estimated treatment difference (Aredia - placebo) in median SMR(-HCM) improved from -1.0/yr by the end of the core phase to -1.8/yr by the end of the extension phase. Similarly, the estimated treatment difference (Aredia - placebo) in proportion of patients with at least one SRE(-HCM) improved from -13% by the end of the core phase to -19% by the end of the extension phase. The estimated treatment difference in median time to first SRE(-HCM) increased from 6.1 months to 6.9 months.

In the hormonal therapy trial, however, the estimated difference (Aredia - placebo) in median SMR(-HCM) was -1.0/yr by the end of the core phase and -0.9/yr by the end of the extension phase. Similarly, the estimated difference in proportion of patients with at least one SRE(-HCM) was 8% by the end of the core phase and 8% by the end of the extension phase. The estimated treatment difference in median time to first SRE(-HCM) did not change (3.5 months) from the end of the core phase to the end of the extension phase.

The sponsor proposed to remove the qualifying statements in the indication section of the package insert that states that the effect of Aredia was less pronounced in the hormonally treated patients than in the chemotherapy treated patients. From this reviewer's evaluations summarized in Table 2R, it appeared that the estimated effect of Aredia (seen in numerical differences) by the end of the extension phase is different between the chemotherapy treated patients and the hormonally treated patients. The results of efficacy found at the end of the core phase were consistent with the results based on both phases I and II in terms of statistical evidence. This applies to both chemotherapy treated patients and the hormonally treated patients.

/S/

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Chen

Dr. Chi 7/15/98

cc:
NDA 20-927
HFD-150/Div. File
HFD-150/Dr. Justice
HFD-150/Dr. Williams
HFD-510/Ms Catterson
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Wang
HFD-710/Chron

SWANG/04-22-98/WP60-Aredia2.nda

This review consists of 15 pages of text which includes 6 tables from the sponsor, 4 Reviewer Tables, and an Attachment.

Attachment: Definition of Skeletal Related Episodes (SRE)

Skeletal Related Episodes are defined as any of the following:

(I) pathologic fractures,

(ii) instances of spinal cord compression or collapse,

(iii) surgical procedures for the treatment of pathologic fractures or for the stabilization of impending pathologic fractures,

(iv) surgical procedures for the treatment or prevention of spinal cord compression or collapse,

(v) Radiation therapy for the relief of bone pain,

(vi) radiation therapy for the treatment or prevention of pathologic fractures or spinal cord compression or collapse, and

(vii) episodes of hypercalcemia in which the corrected serum calcium was greater than or equal to 12.0 mg/dl and/or some form of therapy was administered for an abnormal (high) corrected serum calcium.